



Figure S1: Flow diagram illustrating sample sizes for genetic ( $n = 634$ ), epigenetic ( $n = 494$ ), and transcriptomic ( $n = 429$ ) analyses in GENOA AA.

<p><b><u>Genetic associations</u></b></p> <p><b>Model 1:</b> General cognitive function ~ SNP + age at cognition measurement + sex + PC1-4+ familial relatedness (random effect)</p> <p><b>Model 2:</b> Model 1 + educational attainment</p> <p><b>Model 3:</b> Model 2 + <i>APOE</i> <math>\epsilon</math>2 + <i>APOE</i> <math>\epsilon</math>4</p>
<p><b><u>Epigenetic associations</u></b></p> <p><b>Model 1:</b> General cognitive function ~ CpG site + sex + age at cognition measurement + age difference between methylation and cognition measurements + smoking status + PC1-4 + familial relatedness (random effect)</p> <p><b>Model 2:</b> Model 1 + educational attainment</p> <p><b>Model 3:</b> Model 2 + <i>APOE</i> <math>\epsilon</math>2 + <i>APOE</i> <math>\epsilon</math>4</p>
<p><b><u>Genetic-epigenetic interaction associations</u></b></p> <p><b>Model 4:</b> General cognitive function ~ SNP + CpG + SNP*CpG + age at cognition measurement + age difference between methylation and cognition measurements + sex + educational attainment + <i>APOE</i> <math>\epsilon</math>2 + <i>APOE</i> <math>\epsilon</math>4 + smoking status + PC1-4 + familial relatedness (random effect)</p>

Figure S2: Models used to assess genetic, epigenetic and genetic-epigenetic interaction associations with general cognitive function.



**Table S1. Pearson's correlations among the six cognitive measures ( $n = 634$ )**

	RAVLT	DSST	COWA-FAS	SCWT	TMTA	General cognitive function
RAVLT	1.000					
DSST	0.365***	1.000				
COWA-FAS	0.248***	0.516***	1.000			
SCWT	0.251***	0.516***	0.336***	1.000		
TMTA	0.241***	0.663***	0.419***	0.432***	1.000	
General cognitive function	0.522***	0.874***	0.698***	0.704***	0.791***	1.000

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; DSST, Digit Symbol Substitution Task; COWA-FAS, Controlled Oral Word Association Test; SCWT, Stroop Color-Word Test; TMTA, Trail Making Test A

\*\*\* $p < 0.001$

**Table S2. Pearson's correlations among the five sentinel *ABCA7* SNPs (*n* = 634)**

	rs3764647	rs3764650	rs115550680	rs3752246	rs4147929
rs3764647	1.000				
rs3764650	0.843***	1.000			
rs115550680	-0.117**	-0.141***	1.000		
rs3752246	-0.139***	-0.004	-0.101*	1.000	
rs4147929	-0.140***	-0.026	-0.110**	0.956***	1.000

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

**Table S3. Association between *ABCA7* sentinel SNPs and general cognitive function ( $n = 634$ )**

PMID <sup>a</sup>	Ancestry <sup>b</sup>	SNP	Chr	Position	Risk Allele	RAF	Model 1		Model 2		Model 3	
							$\beta_{\text{SNP}}$	$p$ -value	$\beta_{\text{SNP}}$	$p$ -value	$\beta_{\text{SNP}}$	$p$ -value
28480329	AA	rs3764647	19	1044712	G	0.203	-0.04	0.518	-0.02	0.786	-0.01	0.823
21460840	EA	rs3764650	19	1046520	G	0.254	-0.03	0.598	-0.02	0.768	-0.02	0.716
23571587	AA	rs115550680	19	1050420	G	0.060	-0.03	0.748	-0.01	0.928	-0.01	0.884
21460841	EA	rs3752246	19	1056492	G	0.042	0.21	0.088	0.15	0.180	0.15	0.186
24162737	EA	rs4147929	19	1063443	A	0.049	0.21	0.075	0.12	0.243	0.12	0.241
-	-	<i>APOE</i> $\epsilon 2$	19	45411941	T	0.122	0.07	0.317	0.11	0.087	-	-
-	-	<i>APOE</i> $\epsilon 4$	19	45412079	C	0.226	-0.11	0.046*	-0.12	0.022*	-	-

Abbreviations: PMID, Pubmed ID; AA, African American; EA, European American; Chr, chromosome; RAF, risk allele frequency in GENOA

a. Pubmed ID numbers for studies that identified sentinel SNPs in the *ABCA7* region in association with Alzheimer's disease.

b. Ancestry of cohorts in which significant associations were identified between sentinel SNPs in the *ABCA7* region and Alzheimer's disease

Model 1: General cognitive function  $\sim$  SNP + age at cognition measurement + sex + PC1-4 + familial relatedness (random effect)

Model 2: Model 1 + educational attainment

Model 3: Model 2 + *APOE*  $\epsilon 2$  + *APOE*  $\epsilon 4$

\* $p < 0.05$ ; no associations were significant after Bonferroni correction at  $\alpha = 0.05/5 = 0.01$ .

**Table S4. Association of CpGs in the *ABCA7* region and general cognitive function ( $p < 0.05$ ;  $n = 494$ )**

CpG site	Position	Site Type	Relation to CpG Island	Model 1		Model 2		Model 3	
				$\beta_{\text{CpG}}$	$p\text{-value}$	$\beta_{\text{CpG}}$	$p\text{-value}$	$\beta_{\text{CpG}}$	$p\text{-value}$
cg22271697	1042537	Gene Body	North Shelf	0.08	0.009*	0.07	0.007*	0.08	0.004*
cg00874873	1051161	Gene Body	CG Island	0.12	0.074	0.13	0.025*	0.12	0.034*
cg11714200	1065689	Promoter	North Shore	0.06	0.101	0.08	0.030*	0.07	0.037*
cg26264438	1039942	Promoter	CG Island	0.53	0.236	0.84	0.039*	0.83	0.041*
cg12082025	1064219	Gene Body	CG Island	0.05	0.394	0.11	0.047*	0.11	0.042*
cg18644543	1067356	1st Exon; 5' UTR	CG Island	-0.51	0.031*	-0.33	0.132	-0.34	0.118

Model 1: General cognitive function ~ CpG site + sex + age at cognition measurement + age difference between methylation and cognition measurements + smoking status+ PC1-4 + familial relatedness (random effect)

Model 2: Model 1 + educational attainment

Model 3: Model 2 + *APOE*  $\epsilon$ 2 + *APOE*  $\epsilon$ 4

\* $p < 0.05$ ; No associations are significant at FDR  $q < 0.1$

**Table S5. Interaction between *ABCA7* sentinel SNPs and CpG sites on general cognitive function ( $p < 0.05$ ;  $n = 494$ )**

SNP * CpG site Interaction	CpG position	Main effects				Interaction	
		$\beta_{\text{SNP}}$	$p$ -value	$\beta_{\text{CpG}}$	$p$ -value	$\beta_{\text{interaction}}$	$p$ -value
rs3764647 * cg00135882	1065783	-0.01	0.875	0.24	0.086	-0.80	$1.46 \times 10^{-4}$ **
rs115550680 * cg06169110	1046615	-0.23	0.045*	0.06	0.143	-0.38	$2.18 \times 10^{-4}$ **
rs115550680 * cg17316918	1056930	-0.05	0.661	-0.06	0.164	0.41	$4.84 \times 10^{-4}$ **
rs3764647 * cg22271697	1042537	-0.07	0.319	0.16	$7.23 \times 10^{-6}$ *	-0.18	$5.77 \times 10^{-4}$ **
rs115550680 * cg05372495	1063625	-0.04	0.707	$4.92 \times 10^{-3}$	0.837	0.17	0.008*
rs115550680 * cg02913166	1041178	-0.10	0.329	-0.02	0.244	0.17	0.010*
rs115550680 * cg09467711	1037732	-0.26	0.049*	-0.01	0.632	0.10	0.011*
rs115550680 * cg12817436	1068561	-0.01	0.961	-0.02	0.376	0.20	0.011*
rs115550680 * cg07726048	1039944	-0.03	0.799	0.30	0.031*	-1.02	0.012*
rs115550680 * cg07690733	1066986	-0.11	0.301	-0.14	0.60	2.27	0.014*
rs115550680 * cg07325521	1040062	-0.02	0.872	-0.12	0.627	-1.50	0.015*
rs3764647 * cg09467711	1037732	-0.07	0.315	0.03	0.109	-0.07	0.017*
rs3752246 * cg06169110	1046615	$4.94 \times 10^{-3}$	0.967	-0.02	0.597	0.24	0.033*

Model 4: General cognitive function ~ SNP + CpG + SNP\*CpG + age at cognition measurement + age difference between methylation and cognition measurements + sex + educational attainment + *APOE*  $\epsilon 2$  + *APOE*  $\epsilon 4$  + smoking status + PC1-4 + familial relatedness (random effect)

\*  $p < 0.05$ ; \*\* FDR  $q < 0.1$



**Table S6. Pearson's correlations among *ABCA7* CpG sites<sup>a</sup> (*n* = 494)**

	cg00135882	cg22271697	cg06169110	cg17316918	cg00874873	cg11714200	cg26264438	cg12082025	cg18644543
cg00135882	1.000								
cg22271697	0.243***	1.000							
cg06169110	0.273***	0.085	1.000						
cg17316918	0.114*	0.152***	-0.051	1.000					
cg00874873	0.056	0.166***	0.037	0.216***	1.000				
cg11714200	0.128**	0.173***	-0.039	0.213***	0.139**	1.000			
cg26264438	-0.291***	-0.119**	-0.105*	-0.259***	-0.091*	-0.104*	1.000		
cg12082025	0.400***	0.121**	0.217***	0.151***	0.043	0.070	-0.223***	1.000	
cg18644543	-0.220***	-0.130**	0.041	-0.380***	-0.235***	-0.152***	0.407***	-0.125**	1.000

a. CpG sites in this correlation matrix were chosen from Tables 2 and S4. Cg00135882, cg22271697, cg06169110 and cg17316918 are significant CpG sites in the SNP-by-CpG interactions on general cognitive function (FDR  $q < 0.1$ ; Table 2). Cg22271697, cg00874873, cg11714200, cg26264438, cg12082025 and cg18644543 are nominally associated with general cognitive function ( $p < 0.05$ ; Table S4).

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

**Table S7. Estimated effect of CpG site on general cognitive function for given *ABCA7* SNP genotype group, after excluding outlying values for CpG sites<sup>a</sup>**

SNP	CpG site	Genotype	$\beta_{\text{CpG}}$	<i>p</i> -value
rs3764647	cg00135882	AA	0.14	0.311
		GG/AG	-0.49	0.005*
rs3764647	cg22271697	AA	0.14	1.00×10 <sup>-4</sup> *
		GG/AG	-0.02	0.719
rs115550680	cg06169110	AA	0.06	0.130
		GG/AG	-0.37	2.00×10 <sup>-4</sup> *
rs115550680	cg17316918	AA	-0.05	0.238
		GG/AG	0.33	0.004*

a. Outliers greater or less than 4 standard deviations were excluded: 4 values were excluded for cg00135882 (*n* = 490), 2 values were excluded for cg22271697 (*n* = 492) and cg17316918 (*n* = 492), and 1 value was excluded for cg06169110 (*n* = 493)

Model 4: General cognitive function~ SNP + CpG + SNP\*CpG + age at cognition measurement + age difference between methylation and cognition measurements + sex + educational status + *APOE* ε2 + *APOE* ε4 + smoking status + PC1-4 + familial relatedness (random effect)

\* *p*<0.05

**Table S8. Estimated effect of CpG<sup>a</sup> site on general cognitive function for given *ABCA7* SNP genotype group, after adjusting for SNP effect**

SNP	CpG site	Genotype	$\beta_{\text{CpG}}$	<i>p</i> -value
rs3764647	cg22271697	AA	0.15	$1.00 \times 10^{-4}$ *
		GG/AG	-0.02	0.571
rs115550680	cg06169110	AA	0.06	0.120
		GG/AG	-0.37	$2.00 \times 10^{-4}$ *

a. Sensitivity analysis was conducted on identified SNP-by-CpG interactions from Table 2 whose CpGs were associated with their corresponding SNPs ( $P < 0.05$ ). The SNP effect was adjusted out of the CpG site effect, and the interaction analysis was conducted using the adjusted CpG value

Model 4: General cognitive function ~ SNP + CpG + SNP\*CpG + age at cognition measurement + age difference between methylation and cognition measurements + sex + educational status + *APOE*  $\epsilon 2$  + *APOE*  $\epsilon 4$  + smoking status + PC1-4 + familial relatedness (random effect)

\*  $p < 0.05$

**Table S9: Interaction between *ABCA7* sentinel SNPs and CpG sites on neurocognitive measurements (*n* = 494)**

DSST	Main effects				Interaction	
	$\beta_{\text{SNP}}$	<i>p</i> -value	$\beta_{\text{CpG}}$	<i>p</i> -value	$\beta_{\text{interaction}}$	<i>p</i> -value
rs3764647 * cg00135882	-0.35	0.679	0.68	0.709	-7.73	0.005*
rs3764647 * cg22271697	-0.88	0.307	1.22	0.008*	-1.37	0.047*
rs115550680 * cg06169110	-2.19	0.145	0.49	0.340	-4.24	0.002*
rs115550680 * cg17316918	-0.07	0.959	-0.54	0.319	3.38	0.028*

COWA-FAS	Main effects				Interaction	
	$\beta_{\text{SNP}}$	<i>p</i> -value	$\beta_{\text{CpG}}$	<i>p</i> -value	$\beta_{\text{interaction}}$	<i>p</i> -value
rs3764647 * cg00135882	-0.20	0.828	2.85	0.143	-6.79	0.023*
rs3764647 * cg22271697	-0.64	0.488	1.15	0.021*	-1.04	0.158
rs115550680 * cg06169110	-1.67	0.300	0.01	0.978	-1.76	0.219
rs115550680 * cg17316918	-0.59	0.684	0.07	0.905	3.56	0.030*

RAVLT	Main effects				Interaction	
	$\beta_{\text{SNP}}$	<i>p</i> -value	$\beta_{\text{CpG}}$	<i>p</i> -value	$\beta_{\text{interaction}}$	<i>p</i> -value
rs3764647 * cg00135882	0.53	0.055	0.19	0.747	-0.87	0.346
rs3764647 * cg22271697	0.50	0.070	0.27	0.075	-0.48	0.036*
rs115550680 * cg06169110	-0.32	0.511	0.07	0.688	-0.71	0.107
rs115550680 * cg17316918	0.09	0.831	-0.06	0.737	1.20	0.017*

SCWT	Main effects				Interaction	
	$\beta_{\text{SNP}}$	<i>p</i> -value	$\beta_{\text{CpG}}$	<i>p</i> -value	$\beta_{\text{interaction}}$	<i>p</i> -value
rs3764647 * cg00135882	-0.55	0.498	2.92	0.089	-7.68	0.004*
rs3764647 * cg22271697	-1.06	0.187	1.68	1.21×10 <sup>-4</sup> *	-1.79	0.006*
rs115550680 * cg06169110	-2.70	0.058	0.93	0.056	-3.29	0.009*
rs115550680 * cg17316918	-1.23	0.340	-0.89	0.083	3.52	0.016*

TMTA	Main effects				Interaction	
	$\beta_{\text{SNP}}$	<i>p</i> -value	$\beta_{\text{CpG}}$	<i>p</i> -value	$\beta_{\text{interaction}}$	<i>p</i> -value
rs3764647 * cg00135882	-0.03	0.333	0.05	0.484	-0.23	0.043*
rs3764647 * cg22271697	-0.05	0.143	0.06	0.002*	-0.07	0.020*
rs115550680 * cg06169110	-0.08	0.187	0.02	0.423	-0.15	0.006*
rs115550680 * cg17316918	-0.01	0.903	-0.02	0.272	0.11	0.089

Key: DSST, Digit Symbol Substitution Task; COWA-FAS, Controlled Oral Word Association Test; RAVLT, Rey Auditory Verbal Learning Test; SCWT, Stroop Color-Word Test; TMTA, Trail Making Test A

Model 4: Cognitive test score ~ SNP + CpG + SNP\*CpG + age at cognition measurement + age difference between methylation and cognition measurements + sex + educational attainment + *APOE*  $\epsilon$ 2 + *APOE*  $\epsilon$ 4 + smoking status + PC1-4 + familial relatedness (random effect)

\* *p*<0.05

**Table S10. Interaction between *ABCA7* sentinel SNPs and CpG sites<sup>a</sup> on transcripts in the *ABCA7* gene region ( $p < 0.05$ ;  $n = 429$ )**

Transcript	SNP * CpG site Interaction	Main effects				Interaction	
		$\beta_{\text{SNP}}$	$p$ -value	$\beta_{\text{CpG}}$	$p$ -value	$\beta_{\text{interaction}}$	$p$ -value
ENST00000525939	rs115550680 * cg17316918	0.03	0.428	$-9.82 \times 10^{-3}$	0.493	0.09	0.026*
ENST00000531467	rs3764647 * cg22271697	0.03	0.085	-0.012	0.270	0.03	0.046*

Model 5: Transcript  $\sim$  SNP + CpG + SNP\*CpG + age at gene expression measurement + age difference between methylation and gene expression measurements + sex + PC1-4 + familial relatedness (random effect)

a. Significant SNP-by-CpG interactions in Table 2

\*  $p < 0.05$ ; No associations are significant at FDR  $q < 0.1$

**Table S11. Estimated effect of CpG site on *ABCA7* transcripts for given *ABCA7* SNP genotype group (*n* = 429)**

Transcript <sup>a</sup>	SNP	CpG site	Genotype	$\beta_{\text{CpG}}$	<i>p</i> -value
ENST00000531467	rs3764647 <sup>b</sup>	cg22271697	AA	-0.01	0.319
			GG/AG	0.02	0.120
ENST00000525939	rs115550680 <sup>c</sup>	cg17316918	AA	$-7.6 \times 10^{-3}$	0.597
			GG/AG	0.07	0.054

a. Transcripts associated with previously identified SNP-by-CpG interactions in Table S10

b. GG (*n* = 15) and AG (*n* = 156) groups were combined in the GG/AG group (*n* = 151)

c. GG (*n* = 3) and AG (*n* = 47) were combined in the GG/AG group (*n* = 50)

Model 5: Transcript ~ SNP + CpG + SNP\*CpG + age at gene expression measurement + age difference between methylation and gene expression measurements + sex + PC1-4 + familial relatedness (random effect)

No associations are significant at  $p < 0.05$

**Table S12. Association of SNPs<sup>a</sup> on transcripts in the *ABCA7* gene region ( $p < 0.05$ ;  $n = 429$ )**

Transcript	SNP	$\beta_{\text{SNP}}$	$p$ -value
ENST00000531467	rs115550680	-0.13	$3.17 \times 10^{-5}^{**}$
ENST00000527496	rs115550680	-0.13	$2.14 \times 10^{-4}^{**}$
ENST00000529442	rs115550680	-0.10	$5.07 \times 10^{-4}^{**}$
ENST00000524850	rs115550680	-0.09	0.001 <sup>**</sup>
ENST00000526885	rs115550680	-0.06	0.008 <sup>**</sup>
ENST00000532194	rs115550680	-0.07	0.009 <sup>**</sup>
ENST00000433129	rs115550680	-0.06	0.012 <sup>**</sup>
ENST00000525238	rs115550680	-0.06	0.012 <sup>**</sup>
ENST00000263094	rs115550680	-0.05	0.015 <sup>**</sup>
ENST00000530703	rs115550680	-0.06	0.024 <sup>**</sup>
ENST00000435683	rs115550680	-0.05	0.026 <sup>**</sup>
ENST00000530703	rs3764647	0.03	0.037 <sup>*</sup>

Model 5: Transcript  $\sim$  SNP + age at gene expression measurement + sex + PC1-4 + familial relatedness (random effect)

a. SNPs shown were previously significant in the SNP-by-CpG interactions in Table 2

\*  $p < 0.05$ , \*\* FDR  $q < 0.1$

**Table S13. Association of CpG sites<sup>a</sup> on transcripts in the *ABCA7* region ( $p < 0.05$ ;  $n = 429$ )**

Transcript	CpG Site	$\beta_{\text{CpG}}$	$p$ -value
ENST00000531478	cg06169110	0.02	0.008*
ENST00000526885	cg06169110	0.02	0.037*

Model 5: Transcript  $\sim$  CpG + age + age difference between methylation measurement and gene expression measurement + sex + PC1-4 + familial relatedness (random effect)

a. CpG sites shown were previously significant in the SNP-by-CpG interactions in Table 2

\* $p < 0.05$ ; No associations are significant at FDR  $q < 0.1$